AHRQ Comparative Effectiveness Review Surveillance Program

CER # 26: Therapies for Children with Autism Spectrum Disorders (ASDs)

Original release date: April, 2011

Surveillance Report, 1st Assessment: January, 2012
Surveillance Report, 2nd Assessment: October, 2012

Key Findings, 1st Assessment:

- For Key Question 1, conclusions regarding intensive early intervention, educational, medical, and allied health interventions are still valid. Original conclusion regarding insufficient evidence for parent training is possibly out of date due to two new high quality RCTs, one with six month followup and the other with one year. Original conclusion regarding insufficient evidence for social skills training for older children is possibly out of date due to three new RCTs. Original conclusion regarding Complementary and Alternative Medicine (CAM) may possibly be out of date due to new systematic review on massage therapy which includes four RCTs.
- For Key Question 2, conclusions are still valid, with the exception of impact of provider type, which may possibly be out of date.
- Conclusions are still valid for Key Questions 3 through 7.

Key Findings, 2nd Assessment:

- For Key Question 1, conclusions regarding educational, medical, and allied health interventions are still valid.
- Original conclusions regarding low strength of evidence for Early Intensive Behavioral Interventions (EIBI) are possibly out of date due to new RCTs and long-term follow-up of previously included studies.
- Original conclusion regarding insufficient evidence for parent training is possibly out of date due to several new RCTs.
- Original conclusion regarding insufficient evidence for social skills training for school age children is probably out of date due to many new RCTs.
- Original conclusion regarding Complementary and Alternative Medicine (CAM) may possibly be out of date due to new systematic review on massage therapy which includes four RCTs.
- For Key Question 2, conclusions are still valid, with the exception of impact of provider type, which may possibly be out of date.
- Conclusions are still valid for Key Questions 3 through 7.

Summary Decision

This CER's priority for updating is **Medium**. This has increased from low in the 1st assessment.

Authors:
Margaret Maglione, MPP
Aneesa Motala, BA
Roberta Shanman, MLS
Sydne Newberry, PhD
Jennifer Schneider Chafen, MS, MD
Paul Shekelle, MD, PhD

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

Subject Matter Experts

Susan Levy, MD

University of Pennsylvania

Tristam Smith, PhD

University of Rochester

Contents

Table

Comparative Effectiveness of Therapies for Children with Autism Spectrum Disorders (ASDs)

1. Introduction

Comparative Effectiveness Review (CER) # 26 was originally released in April, 2011.[1] The 1st assessment, completed in January, 2012, found a "low" need to update the CER. The current assessment was completed in October, 2012.

2. Methods

2.1 Literature Searches

For the 1st assessment, we conducted a limited literature search covering January, 1, 2009 to October 20, 2011, using the identical search strategy used for the original report. This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Autism, Journal of Autism and Developmental Disorders, Pediatrics, Journal of Child Psychiatry and Psychology, and American Journal of Speech and Language Pathology). The specialty journals were those most highly represented among the references for the original report. This search resulted in only 14 titles to review. Thus, a full search of Pubmed and PsycInfo was undertaken to ensure no relevant studies were missed, and a full search was conducted again for the 2nd assessment. The latter search covered January, 2011 to August, 2012. Appendix A includes the search strategy.

2.2 Study selection

We used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

For the 1st assessment, we shared the conclusions of the original report with nine experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members) for their opinion on the need to update the report and their recommendations of any relevant new studies; the EPC lead authors and four subject matter experts responded. Only two experts responded to our request for the 2nd assessment. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

The authors of the original CER did not conduct meta-analyses due to low number of studies, and heterogeneity of interventions and outcomes. The new studies identified did make meta-analysis possible. Thus, findings were summarized qualitatively.

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that includes the key questions, the original conclusions, the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. We categorized whether the conclusions need updating using a 4-category scheme:

- Original conclusion is still valid and this portion of the CER does not need updating
- Original conclusion is possibly out of date and this portion of the CER may need updating
- Original conclusion is probably out of date and this portion of the CER may need updating
- Original conclusion is out of date.

We used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?

- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

In the 1st assessment, the literature search identified 166 titles. After title and abstract review, we selected twelve for full text review. The remaining 153 were rejected because they were editorials, letters, animal studies, individual case reports, or did not include topics of interest. Strangely, the search results included many topics unrelated to ASDs, such as hospital acquired infections, Parkinson's disease, disk herniation, and cancer. Fourteen additional articles were reviewed at the suggestion of the experts.

In total, 26 articles went on to full text review. Eleven articles were rejected because they had already been included in or rejected from the original CER or did not include an outcome within the scope of the CER. The remaining 15 studies were abstracted into an evidence table.[2-16]

The literature search for the 2nd assessment identified 103 titles. After title and abstract review, we selected 43 for full text review. Ten additional articles were suggested by experts. Of these 53, 31 met our inclusion criteria and were abstracted into an evidence table (see Appendix B).[17-47] The other 22 were non-systematic reviews, single subject research, letters to the editor, or program descriptions with no child outcomes reported.

3.2 Expert Opinion

Two Technical Expert Panel members responded to our request for input. They felt that the majority of the CER conclusions were still valid, but some conclusions on specific intervention types needed to be updated due to new research findings.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions and the conclusions of the original report in the first column. These are followed by the results of the literature search, any data from the FDA or similar regulatory agencies, and the experts' opinions from both the 1st and 2nd assessments. Finally, the right-hand column contains the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update.

In sum, seven of the 25 conclusions are possibly out of date, and another is probably out of date. The results of several randomized controlled trials of interventions for children with ASD have been published since the CER was released in April, 2011. Regarding Key Question 1, the

strength of evidence on early intensive behavioral intervention (EIBI), parent training, and social skills programs for high functioning school age children may have increased. However, few studies on modifiers of treatment outcomes (Key Question 2) have been published. No new studies on early results or end of treatment effects that predict outcomes (Key Questions 3 & 4) were identified.

Table 1: Summary Table. Second Assessment: Therapies for Children with Autism Spectrum Disorders

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
Key Question 1: : Effects of Treatment on Core and Commonly Associated Symptoms in Children With ASDs: Behavioral Interventions						
Behavioral interventions. Early intensive behavioral and developmental intervention may improve core areas of deficit for individuals with ASDs; however, few randomized controlled trials (RCTs) of sufficient quality have been conducted, no studies directly compare effects of different treatment approaches, and little evidence of practical effectiveness or feasibility exists.	**January 2012 -**We found one RCT that compared two different approaches, although the second approach was a social recreational program more similar to control group than a well-designed intervention. We also found an RCT comparing an intensive behavioral intervention with and without a specific component. Results, described in the relevant sections below, were not sufficient to change the original CER conclusion. **October 2012** – We found no studies comparing different EIBI approaches. In addition to 2-year evidence on an EIBI controlled trial in Norway (see below) we found one case series (Klintwall, 2012) and two controlled trials (Strauss, 2012; Flanagan, 2012) of EIBI that reported significant improvements in ASD severity, behavior, language, and cognitive skills.	NA	**January 2012 -** Three experts agreed the conclusion was still valid. **October 2012** – Two experts suggested 3 new studies that might increase the strength of evidence.	**January 2012** – Conclusion still valid. **October 2012** – Conclusion possibly out of date and this portion of CER may need updating.	Up-to-date	Possibly out-of-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
Studies of UCLA/Lovaas-based interventions report greater improvements in cognitive performance, language skills, and adaptive behavior skills than broadly defined eclectic treatments available in the community. However, strength of evidence is currently low. Further, not all children receiving intensive intervention demonstrate rapid gains, and many children continue to display substantial impairment.	**January 2012 -**No new studies were identified. However, we did identify long term follow-up (f/u) of two studies included in the original CER. An RCT comparing university based vs home-based intensive behavioral intervention vs control reported that when baseline scores were controlled there were significant difference in improvement by group at 2 years post-intervention. (Kovshoff, 2001). A 7 year f/u of a cohort who attended intensive behavioral intervention found that although children with ASDs acquired new skills and abilities post intervention, they did so at a rate slower than their typically developing peers (Magiati, 2011). **October 2012** – A controlled trial of intensive intervention in preschool in Norway (Eikeseth, 2012; Eldevik, 2012) reported that the intervention group had greater improvement in various behaviors at 2 year follow up compared to control group.	NA	**January 2012 -** One expert suggested two reports on long term follow-up of studies included in the original CER, but felt the conclusion was still valid. The two other experts felt the conclusion was still valid. **October 2012 –** One expert suggested two studies with long term (>= 2 years) follow-up that might increase the strength of evidence. These were actually publications on the same study (Eikeseth, 2012; Eldevik, 2012).	**January 2012 -** Conclusion still valid. **October 2012** – Conclusion possibly out of date and this portion of CER may need updating.	Up-to-date	Possibly out-of-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
Although positive results are reported for the effects of intensive interventions that use a developmental framework, such as the Early Start Denver Model (ESDM), evidence for this type of intervention is currently insufficient because few studies have been published to date.	**January 2012 -**No new studies of intensive interventions with a developmental framework were identified. An RCT of a less intensive DIR-based developmental social pragmatic (DSP) intervention (2 hours per week per family) vs community tx reported significant effect on attention to activity, involvement, and initiation of join attention. However, effects on standard language assessments were insignificant. (Casenhiser, 2011). **October 2012** – An RCT of parent-delivered ESDM vs usual care showed no difference in child outcomes. (Rogers, 2012). An RCT of another developmental approach (DIR/floortime) showed greater reduction of ASD symptoms compared to control group (Pajareya, 2011).	NA	**January 2012 -** One expert suggested new studies but felt the conclusion didn't change. The two other experts felt the conclusion was still valid. **October 2012** – Both experts suggested a study that might increase the strength of evidence (Rogers, 2012).	**January 2012** – Conclusion still valid. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date
Less intensive interventions providing parent training for bolstering social communication skills and managing challenging behaviors have been associated in individual studies with short-term gains in social communication and language use. The	**January 2012 -**One new RCT reported that "focus" training for parents had no significant intervention effects on language, global clinical improvement, or parental skills. (Oosterling, 2010). One RCT of caregiver mediated joint engagement vs wait list (Kasari, 2010) reported greater improvement on 2 of 3 joint engagement outcomes, one of	NA	**January 2012 -** One expert suggested two new studies but felt the conclusion didn't change. The two other experts felt the conclusion was still valid. **October 2012** –One expert suggested two articles which actually fit into the social skills section below. Another expert suggested the Kasari, 2010 study included in our January 2012 update.	**January 2012** – Conclusion possibly out of date and this portion of CER may need updating. Two new studies report joint attention outcomes (as do several in the original CER); these new studies are of better quality and include longer term f/u. **October 2012 -**	Possibly out-of-date	Possibly out-of-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
current evidence base for such treatment remains insufficient, with current research lacking consistency in interventions and outcomes assessed.	two join attention skills outcomes and one of two play quality outcomes. Gains were maintained at 1 year f/u. An RCT of a comprehensive intervention with an "Interpersonal Synchrony" component added (Landa, 2011) versus without found a significant effect on "socially engaged imitation" that was maintained for 6 months and transferred to other contexts. However, effect on initiation of joint attention was not significant. A small case series on Project ImPACT, a school based training for parents, showed that social impairment decreased significantly according to teacher report. (Ingersoll, 2011) **October 2012** – A small case series (N=17) of parents given pivotal response training reported child functional verbal utterances increased significantly from baseline to week 10 (Minjarez, 2010). A small RCT reported that Reciprocal Imitation Training group made significantly more gains in elicited imitation and spontaneous imitation than a control group (Ingersall, 2010). An RCT reported that a group receiving Joint Attention			Conclusion possibly out of date and this portion of CER may need updating.		

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
	training in preschool showed more improvement in attention with teachers and mothers than children with preschool alone. (Kaale, 2012) One small RCT reported that children receiving JASPER (Joint Attention Symbolic Play Engagement and Regulation) added to an intensive ABA program initiated more gestures and spent less time unengaged than children who received the ABA alone. (Goods, 2012)					
Although all of the studies of social skills interventions reported some positive results, most have not included objective observations of the extent to which improvements in social skills generalize and are maintained within everyday peer interactions. Strength of evidence is insufficient to assess effects of social skills training on core autism outcomes for older children or play- and interaction-based approaches for younger children.	**January 2012 -**We identified 3 new RCTs of programs for older children. In one RCT, the UCLA Peers program reported significantly greater changes in parent reported SSRS social skills total, cooperation, and responsibility scales versus wait list. Most gains remained 14 weeks post treatment (Laugeson, 2011). However, another RCT of social skills groups using peer tutors reported no significant difference in change in social skills (as measured by the Social Competence Inventory) compared to wait list group (Konening, 2010). An RCT of a Theory of Mind (ToM) intervention vs wait list control reported significantly greater conceptual Theory of Mind	NA	**January 2012 -** One expert suggested two new studies but felt the conclusion didn't change. The two other experts felt the conclusion was still valid. **October 2012** – One expert suggested a new study and a study already included in our January 2012 update. The other expert also suggested studies included in our January 2012 update.	**January 2012** - Conclusion possibly out of date regarding social skills training for older children and this portion of CER may need updating. **October 2012** - Conclusion probably out of date.	Possibly out-of-date	Probably out-of-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
	skills, but elementary understanding, empathic skills and parent reported social behavior did not improve more than control group (Begeer, 2011). **October 2012** – Several new RCTs (Kasari, 2012; Lopata, 2010; DeRosier, 2010) and small CCTs (Castorina, 2011; Lerner, 2011) with children aged 6 through 14 report improvement on validated social skills measurements (SRS, DANVA), as do two small case series (Stichter, 2010; deBruin, 2012).					
Several studies suggest that interventions based on cognitive behavioral therapy are effective in reducing anxiety symptoms. Strength of evidence for these interventions, however, is insufficient pending further replication.	**January 2012 -** One new RCT of cognitive behavioral therapy (CBT) vs a social recreational program showed no significant group difference in anxiety reduction. Both groups showed significant reductions. (Sung, 2011). **October 2012** – An RCT of group CBT with 7 to 14 year olds reported significant improvement in anxiety symptoms (Reaven, 2012).	NA	**January 2012 -** Three experts felt conclusions still valid. **October 2012** – Two experts felt conclusions still valid.	**January 2012** - Conclusion still valid. **October 2012** – Conclusion possibly out of date.	Up-to-date	Possibly out-of-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
Educational interventions. Most research on the Treatment and Education of Autistic and Communication related handicapped CHildren (TEACCH) program was conducted prior to the date cutoff for our review. Newer studies continue to report improvements among children in motor, eye-hand coordination, and cognitive measures. The strength of evidence for TEACCH, as well as broad-based and computer-based educational approaches to affect any individual outcomes is insufficient because there are too few studies and they are inconsistent in outcomes measured.	**January 2012 -**No new studies on TEACCH or similar interventions were identified. **October 2012** – One large RCT (Boyd, 2012) found no significant differences between TEACCH, LEAP, and control group. Another large RCT (Strain, 2011) found that children in LEAP classrooms showed improvements in problem behavior and higher cognitive, language, and social skills. A follow-up (Stahmer, 2011) of a case series (Stahmer, 2004) on Children's Toddler School, an inclusive classroom, reported significant gains in adaptive behavior and communication. A small case series (N = 17) using interest-based learning reported that children in high interest based group made significantly more progress on language and social skills (Dunst, 2011).	NA	**January 2012 -** Three experts agreed conclusion is still valid. **October 2012** – One expert suggested the new study showing no significant differences between TEACCH and LEAP. Another suggested an RCT which actually fell into another category above (joint attention intervention).	**January 2012 -** Conclusion still valid. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date
Medical and related interventions. Although no current medical interventions demonstrate clear benefit for social or communication symptoms, a few			**January 2012 -** One expert reported that unpublished studies presented at conferences reported arbaclofen may improve social withdrawal. Another expert suggested a non systematic review which supported the original CER conclusion. The	**January 2012 -** Conclusion still valid; we found no published studies of arbaclofen in patients with ASDs. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
medications show benefit for repetitive behaviors or associated symptoms.			other expert felt the original conclusion did not change. **October 2012** – Both experts felt conclusion still valid.			
The clearest evidence favors the use of medications to address challenging behaviors. The antipsychotics risperidone and aripiprazole each have at least two RCTs demonstrating improvement in a parent-reported measure of challenging behavior. A parent reported hyperactivity and noncompliance measure also showed significant improvement. In addition, repetitive behavior showed improvement with both risperidone and aripiprazole. Both medications also cause significant side effects, however, including marked weight gain, sedation, and risk of extrapyramidal symptoms (side effects, including muscle stiffness or tremor, that	**January 2012 -**We identified no new studies of the efficacy of atypical antipsychotics in children with ASDs. A systematic review of weight gain and metabolic risk in children using atypical antipsychotics reported that pharmcoepidemiologic work indicates that antipsychotic polypharmacy in children increases the risk for obesity and any cardiovascular, cerebrovascular, or hypertensive adverse event. One included cohort study reported that, perhaps due to less prior antipsychotic exposure, children with ASD have greater weight gain than those taking the drugs for bipolar disorder or schizophrenia. **October 2012** – No new studies of antipsychotics identified.	**January 2012** -In April 2011, the FDA added warnings for quetiapine fumarate, which is often used off-label in children with ASDs: a) tradive dyskinesia may arise after discontinuation and b) decrease in hemoglobin to <= 13 g/dl in males and <=12 g/dl in females has been reported. In January 2011,	**January 2012 -** Three experts agreed conclusion still valid. **October 2012** – Both experts agreed conclusion still valid.	**January 2012 -** Conclusion still valid; as strength of evidence for adverse effects was rated as high in original CER. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
occur in individuals taking antipsychotic medications). These side effects limit use of these drugs to patients with severe impairment or risk of injury.		warnings regarding increased blood pressure in children and hyperglycemia and hyperlidemia in adults. **October 2012** – No new data.				
We rated the strength of evidence as high for the adverse effects of both medications, moderate for the ability of risperidone to affect challenging behaviors, and high for aripiprazole's effects on challenging behaviors.			**January 2012 -** One expert felt the evidence for aripiprazole and behaviors should not be rated higher than the evidence for risperidone. Two experts felt the conclusion was still valid. **October 2012** - Both experts agreed conclusion still valid.	**January 2012** - Conclusion still valid; as strength of evidence for adverse effects was rated as high in original CER, and we found no new efficacy studies. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date
Strength of evidence for melatonin is insufficient.	**January 2012 -** A new meta-analysis of 5 RCTs found melatonin associated with significant improvement in sleep onset and duration. **October 2012** – No new studies identified	NA	NA	**January 2012** - Conclusion possibly out of date and this portion of CER may need to be updated, if stakeholders feel sleep onset and duration are important outcomes. **October 2012** – Conclusion still valid	Possibly out-of-date	Possibly out-of-date
Strength of evidence for Omega 3 fatty acids is insufficient.	**January 2012 –** No new studies identified. **October 2012** - One small	NA	NA	**January 2012 –** Conclusion still valid. **October 2012** –	Up-to-date	Up-to-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
	RCT (N=27) reported no difference in hyperactivity scores between intervention and placebo group.			Conclusion still valid.		
Allied health. The allied health interventions reviewed here varied; the research provided little support for their use.						
All studies of sensory integration and music therapy were of poor quality, and two fair-quality studies of auditory integration showed no improvement associated with treatment.	**January 2012 -** No new studies found. **October 2012** – No new studies found.	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012** –Both experts agreed conclusion still valid.	**January 2012** - Conclusion still valid. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date
Language and communication interventions (Picture Exchange Communication System [PECS] and Responsive Education and Prelinguistic Milieu Training [RPMT]) demonstrated short-term improvement in word acquisition without effect durability, and should be studied further. No other allied health interventions had adequate research to assess the strength of evidence.	**January 2012 -** One RCT of Hanen's "More than Words," language program reported there were no main effects of the intervention at 9 month follow-up. (Carter, 2011) **October 2012** - One RCT of FaceSay computer program reported improved emotion recognition and social interactions in low functioning children. One RCT of Let's Face It! computer game reported in improvements in face recognition. One small controlled trial of PECS vs conventional language therapy, both within TEACCH preschool, reported significantly improvements VABS social scale scores in favor of the PECS group.	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012** – Both experts agreed conclusion still valid. One suggested a new study of PECS (Lerna, 2012).	**January 2012** - Conclusion still valid. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
CAM. Evidence for CAM interventions is insufficient for assessing outcomes.	**January 2012 -** One systematic review of massage therapy (Lee, 2011) included 4 RCTs. One found that massage plus conventional language therapy was superior to language therapy alone for symptom severity and communication attitude. Two RCTs found massage improved sensory profile, adaptive behavior, language, and social abilities compared to a special ed program. A fourth RCT reported effects on social communication. **October 2012** – A systematic review of 5 studies (3 case reports, 1 cohort, 1 RCT) of spinal manipulation showed insufficient evidence to draw conclusions.	NA	**January 2012 -** One expert felt emerging evidence supports inefficacy of diet interventions. (No specific studies were cited.) Two experts felt conclusion still valid. **October 2012** – Both experts agreed conclusion still valid. One suggested a study of Shaolin diet (Chan, 2012). However, standardized outcome assessments were not used in that study.	**January 2012** – Conclusion possibly out of date and this portion of CER (regarding massage) may need updating. **October 2012** – No change from above.	Possibly out-of-date	Possibly out-of-date
Key Question 2. Modifiers of Treatment Outcomes						
With rare exceptions, few studies are designed or powered to identify modifiers of treatment effect. Although we sought studies of treatment modifiers, only one included study actually demonstrated true treatment modifiers based on appropriate study design and statistical analysis. One other study was designed to examine the role of provider on outcomes but showed no difference, possibly because it was underpowered to do so.						
This first study included an analysis of initial characteristics of the children, demonstrating that children who were low in initial object exploration benefited more from RPMT, which explicitly teaches play with objects, while children who were	**January 2012 -**The trial of Hanen's More than Words (see above under language and communication interventions) reported that tx effects were moderated by children's baseline object interest. **October 2012 –** No applicable studies identified.	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012** –One expert felt the conclusion was still valid. The other suggested a study (Farmer, 2011) which was included in our February, 2012 surveillance update.	**January 2012 -** Conclusion still valid, as tx modifiers reported in new study support original CER conclusion. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
relatively high in initial object exploration demonstrated more benefit from PECS. An additional analysis showed greater increases in generalized turn-taking and initiating joint attention in the RPMT group than in PECS. The increased benefit in joint attention for RPMT was seen only in children who began the study with at least seven acts of joint attention.						
One study explicitly sought to examine the impact of provider (parent vs. professional) using similar interventions in an RCT. The study did not show a difference in outcomes for children receiving the UCLA/Lovaas protocol-based intervention in a clinical setting vs. at home from highly trained parents.	**January 2012 -** A two-year f/u of this study (Kovshoff, 2011) found that only the parent intervention group maintained some gains. **October 2012** – No studies of impact of type of provider identified.	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012** – Both experts agreed the conclusion is still valid.	**January 2012** - Conclusion possibly out of date and this portion of CER may need updating. **October 2012** –Same as above.	Possibly out-of-date	Possibly out-of-date
Other studies identified potential correlates that warrant further study. Modifiers with potential for further investigation	**January 2012 -** A secondary analysis (Farmer, 2011) of an RCT included in the original CER (Scahill, 2009) found that higher baseline score on the	NA	**January 2012 -** Two experts felt this conclusion is still valid. One expert did not know. **October 2012** - Both experts agreed the conclusion is still	**January 2012** - Conclusion still valid, as modifiers found significant support original CER conclusion.	Up-to-date	Up-to-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
but with currently conflicting data included pretreatment IQ and language skills, and age of initiation of treatment (with earlier age potentially associated with better outcomes). Social responsiveness and imitation skills have been suggested as skills that may correlate with improved treatment response in UCLA/Lovaas treatment, whereas "aloof " subtypes of ASDs may be associated with less robust changes in IQ. Other studies have seen specific improvement in children with PDD-NOS vs. Autistic Disorder diagnoses, which may be indicative of baseline symptom differences. However, many other studies have failed to find a relationship between autism symptoms and treatment response.	Home Situations Questionnaire predicted greater improvement, regardless of tx groups. No other child characteristics predicted improvement although there was a trend toward older children improving more than younger. A long-term f/u of children enrolled in intensive behavioral intervention (Magiati, 2011) found baseline IQ, language, and adaptive skills predicted positive outcomes 7 years post-intervention. **October 2012** – Younger age at entrance and more intervention hours associated with better outcomes in ESDM (Rogers, 2012). In EIBI program (Klintwall, 2012) children with a larger repertoire of socially mediated and reinforced behaviors at baseline benefited more from tx than children with more stereotypical behaviors.		valid.	**October 2012** –- Conclusion still valid, as modifiers found significant support original CER conclusion.		

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
Key Question 3: Early Results in the Treatment Phase That Predict Outcomes						
The literature offers almost no information about specific observations of children that might be made early in treatment to predict long-term outcomes. Some evidence suggests that changes in IQ over the first year of either UCLA/Lovaas-based or ESDM intervention predicts, or accounts for, longer term change in IQ. However, findings also suggest that although gains in the cognitive domain might be identified primarily within the first year of treatment, changes in adaptive behavior in response to these same interventions may occur over a longer timeframe, if they occur at all.	**January 2012 -** No new studies on early results that predict tx outcomes were identified. **October 2012** – No new studies on early results that predict tx outcomes were identified.	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012 -** Both experts agreed the conclusion is still valid.	**January 2012** - Conclusion still valid. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date
Key Question 4: End of Treatment Effects That Predict Outcomes						

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
One study specifically addressed end-of-treatment effects to predict longer range outcomes. The feasibility of such studies was established in this language study, which reported outcomes 12 months postintervention.	**January 2012 -**No new studies on end of tx results that that predict long-term outcomes were identified. **October 2012 -** No new studies on end of tx results that that predict long-term outcomes were identified.	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012 -** Both experts agreed the conclusion is still valid.	**January 2012 -** Conclusion still valid. **October 2012** – - Conclusion still valid.	Up-to-date	Up-to-date
Key Question 5: Generalization of Treatment Effects						
Few studies measured generalization of effects seen in treatment conditions to either different conditions or different locations. Among behavioral studies, those of treatments for commonly associated conditions, such as anxiety, employed outcomes assessment outside the therapeutic environment, with positive results observed. However, in most cases, outcomes are parent reported and not confirmed by direct observation.	**January 2012 -**No new studies on generalization of effects to other settings were identified. **October 2012 -** No new studies on generalization of effects to other settings were identified.	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012 -** Both experts agreed the conclusion is still valid.	**January 2012 -** Conclusion still valid. **October 2012** – - Conclusion still valid.	Up-to-date	Up-to-date
For medical studies, data across classes of medications are likely	**NA**	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012 -** Both experts	**January 2012 -** Conclusion still valid. **October 2012 -**	Up-to-date	Up-to-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
to be transferable outside of the clinic setting, primarily because the outcome measures used in these studies rely on parent report of the subjects' behavior in the home or other settings and are augmented in some studies by teacher report.			agreed the conclusion is still valid.	Conclusion still valid.		
Key Question 6: Drivers of Treatment Effects						
No studies were identified to answer this question.	No new studies identified other than under Key Question 2: Modifiers	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012 -** Both experts agreed the conclusion is still valid.	**January 2012 -** Conclusion still valid. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date
Key Question 7: Treatment Approaches in Children Under Age Two at Risk for Diagnosis of ASDs						
Research on very young children is preliminary, with four studies identified. One good-quality RCT suggested benefit from the use of ESDM in young children, with improvements in adaptive behavior, language, and cognitive outcomes. Diagnostic shifts within the autism spectrum were reported in close to 30	**January 2012 -**We identified only one study where almost all children were under age two. This studied reported no significant intervention effect for Hanen's More than Words language program (Carter, 2011). **October 2012** – Brief ESDM of one hour per week with parents showed no effect on child outcomes compared to control group in children 14 to 24 months of age.	NA	**January 2012 -** Three experts agreed conclusion still valid. **October 2012 -** Both experts agreed the conclusion is still valid.	**January 2012 -** Conclusion still valid. **October 2012** – Conclusion still valid.	Up-to-date	Up-to-date

Conclusions From CER	RAND Literature Search	FDA	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
percent of children but were not associated with clinically significant improvements in ADOS severity scores or other measures.						

Legend: ADOS- Autism Diagnostic Observation Schecule; ASDs- Autism Spectrum Disorders ; CAM- Complementary and Alternative Medicine; CER-Comparative Effectiveness Review; CBT-cognitive behavioral therapy; EPC- Evicence-based Practice Center; ESDM-Early Start Denver Model; DSP-developmental social pragmatic; FDA-Food and Drug Administration; MHRA- Medicines and Healthcare products Regulatory Agency; PDD-NOS- Pervasive Developmental Disorder-Not Otherwise Specified; PECS-Picture Exchange Communication System; RCTs-randomized controlled trials; RPMT-Responsive Education and Prelinguistic Milieu Training; SCEPC-Southern California Evidence-based Practice Center; TEACCH-Treatment and Education of Autistic and Communication related handicapped Children

References

1. Warren Z, Veenstra-VanderWeele J, Stone W, et al. Therapies for Children With Autism Spectrum Disorder. Comparative Effectiveness Review No. 26. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 11-EHC029-EF Agency for Healthcare Resarch and Quality Rockville, MD: April 2011.

2. Begeer S, Gevers C, Clifford P, et al. Theory of Mind training in children with autism: a randomized controlled trial. J Autism Dev Disord. 2011 Aug;41(8):997-1006. PMID 20976617.

3. Carter AS, Messinger DS, Stone WL, et al. A randomized controlled trial of Hanen's 'More Than Words' in toddlers with early autism symptoms. J Child Psychol Psychiatry. 2011 Jul;52(7):741-52. PMID 21418212.

4. Casenhiser DM, Shanker SG, Stieben J. Learning Through Interaction in Children With Autism: Preliminary Data From a Social-Communication-Based Intervention. Autism. 2011 Sep 26PMID 21949005.

5. Farmer C, Lecavalier L, Yu S, et al. Predictors and Moderators of Parent Training Efficacy in a Sample of Children with Autism Spectrum Disorders and Serious Behavioral Problems. J Autism Dev Disord. 2011 Aug 6PMID 21822762.

6. Ingersoll BR, Wainer AL. Pilot Study of a School-Based Parent Training Program for Preschoolers With ASD. Autism. 2011 Nov 15PMID 22087044.

7. Kasari C, Gulsrud AC, Wong C, et al. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. J Autism Dev Disord. 2010 Sep;40(9):1045-56. PMID 20145986.

8. Koenig K, White SW, Pachler M, et al. Promoting social skill development in children with pervasive developmental disorders: a feasibility and efficacy study. J Autism Dev Disord. 2010 Oct;40(10):1209-18. PMID 20204689.

9. Kovshoff H, Hastings RP, Remington B. Two-year outcomes for children with autism after the cessation of early intensive behavioral intervention. Behav Modif. 2011 Sep;35(5):427-50. PMID 21586502.

10. Landa RJ, Holman KC, O'Neill AH, et al. Intervention targeting development of socially synchronous engagement in toddlers with autism spectrum disorder: a randomized controlled trial. J Child Psychol Psychiatry. 2011 Jan;52(1):13-21. PMID 21126245.

11. Laugeson EA, Frankel F, Gantman A, et al. Evidence-Based Social Skills Training for Adolescents with Autism Spectrum Disorders: The UCLA PEERS Program. J Autism Dev Disord. 2011 Aug 20PMID 21858588.

12. Lee MS, Kim JI, Ernst E. Massage therapy for children with autism spectrum disorders: a systematic review. J Clin Psychiatry. 2011 Mar;72(3):406-11. PMID 21208598.

13. Magiati I, Moss J, Charman T, et al. Patterns of change in children with autism spectrum disorders who received community based comprehensive interventions in their pre-school years: a seven year follow-up study. Research in Autism Spectrum Disorders. 2011;5(3):1016-27.

14. Oosterling I, Visser J, Swinkels S, et al. Randomized controlled trial of the focus parent training for toddlers with autism: 1-year outcome. J Autism Dev Disord. 2010 Dec;40(12):1447-58. PMID 20440639.

15. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol. 2011 Sep;53(9):783-92. PMID 21518346.

16. Sung M, Ooi YP, Goh TJ, et al. Effects of cognitive-behavioral therapy on anxiety in children with autism spectrum disorders: a randomized controlled trial. Child Psychiatry Hum Dev. 2011 Dec;42(6):634-49. PMID 21660428.

17. Alcantara J, Alcantara JD. A systematic review of the literature on the chiropractic care of patients with autism spectrum disorder.

Explore (NY). 2011 Nov-Dec;7(6):384-90. PMID 22051563.

18. de Bruin EI, Verheij F. Social skills training in children with PDD-NOS: an exploratory study. Int J Psychiatry Clin Pract. 2012 Mar;16(1):60-7. PMID 22122657.

19. Eikeseth S, Klintwall L, Jahr E, et al. Outcome for children with autism receiving early and intensive behavioral intervention in mainstream preschool and kindergarten settings. Research in Autism Spectrum Disorders. 2012;6(2):829-35. PMID 2012-03990-028. First Author & Affiliation: Eikeseth, Svein.

20. Eldevik S, Hastings RP, Jahr E, et al. Outcomes of behavioral intervention for children with autism in mainstream pre-school settings. Journal of Autism and Developmental Disorders. 2012;42(2):210-20. PMID 2012-02487-007. PMID: 21472360. First Author & Affiliation: Eldevik, Sigmund.

21. Flanagan HE, Perry A, Freeman NL. Effectiveness of large-scale community-based intensive Behavioral Intervention: A waitlist comparison study exploring outcomes and predictors. Research in Autism Spectrum Disorders. 2012;6(2):673-82. PMID 2012-03990-011. First Author & Affiliation: Flanagan, Helen E.

22. Hopkins IM, Gower MW, Perez TA, et al. Avatar assistant: Improving social skills in students with an ASD through a computer-based intervention. Journal of Autism and Developmental Disorders. 2011;41(11):1543-55. PMID 2011-24311-011. PMID: 21287255. First Author & Affiliation: Hopkins, Ingrid Maria.

23. Klintwall L, Eikeseth S. Number and controllability of reinforcers as predictors of individual outcome for children with autism receiving early and intensive behavioral intervention: A preliminary study. Research in Autism Spectrum Disorders. 2012;6(1):493-9. PMID 2011-25855-058. First Author & Affiliation: Klintwall, Lars.

24. Reaven J, Blakeley-Smith A, Culhane-Shelburne K, et al. Group cognitive behavior therapy for children with high-functioning autism spectrum disorders and anxiety: A randomized trial. Journal of Child Psychology and Psychiatry. 2012;53(4):410-9. PMID 2012-04050-010. First Author & Affiliation: Reaven, Judy.

25. Strauss K, Vicari S, Valeri G, et al. Parent inclusion in early intensive behavioral intervention: The influence of parental stress, parent treatment fidelity and parent-mediated generalization of behavior targets on child outcomes. Research in Developmental Disabilities. 2012;33(2):688-703. PMID 2012-00013-050. PMID: 22188793. First Author & Affiliation: Strauss, Kristin.

26. Kasari C, Rotheram-Fuller E, Locke J, et al. Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders. J Child Psychol Psychiatry. 2012 Apr;53(4):431-9. PMID 22118062.

27. Strain PS, Bovey EH. Randomized control trial of the LEAP model of early intervention for young children with autism spectrum disorders. Topics in Early Childhood Special Education. 2011;31:133-54.

28. Pajareya K, Nopmaneejumruslers K. A pilot randomized controlled trial of DIR/Floortime parent training intervention for pre-school children with autistic spectrum disorders. Autism. 2011 Sep;15(5):563-77. PMID 21690083.

29. . Efficacy of the LEAP and TEACCH Comprehensive Treatment Models for Preschoolers with ASD. Presentation at the International Meeting for Autism Research; May 2012.

30. Bent S, Bertoglio K, Ashwood P, et al. A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. J Autism Dev Disord. 2011 May;41(5):545-54. PMID 20683766.

31. Castorina LL, Negri LM. The inclusion of siblings in social skills training groups for boys with Asperger syndrome. J Autism Dev Disord. 2011 Jan;41(1):73-81. PMID 20461452.

32. DeRosier ME, Swick DC, Davis NO, et al. Efficacy of a Social Skills Group Intervention for improving social behaviors in children with High Functioning Autism Spectrum disorders. J Autism Dev Disord. 2011 Aug;41(8):1033-43. PMID 21042870.

33. Dunst CJ, Trivette CM, Masiello T. Exploratory investigation of the effects of interest-based learning on the development of young children with autism. Autism. 2011 May;15(3):295-305. PMID 21430019.

34. Ingersoll B. Pilot randomized controlled trial of Reciprocal Imitation Training for teaching elicited and spontaneous imitation to children with autism. J Autism Dev Disord. 2010 Sep;40(9):1154-60. PMID 20155309.

35. Kaale A, Smith L, Sponheim E. A randomized controlled trial of preschool-based joint attention intervention for children with autism. J Child Psychol Psychiatry. 2012 Jan;53(1):97-105. PMID 21883204.

36. Karkhaneh M, Clark B, Ospina MB, et al. Social Stories to improve social skills in children with autism spectrum disorder: a systematic review. Autism. 2010 Nov;14(6):641-62. PMID 20923896.

37. Lerner MD, Mikami AY, Levine K. Socio-dramatic affective-relational intervention for adolescents with asperger syndrome & high functioning autism: pilot study. Autism. 2011 Jan;15(1):21-42. PMID 20923890.

38. Lopata C, Thomeer ML, Volker MA, et al. RCT of a manualized social treatment for high-functioning autism spectrum disorders. J Autism Dev Disord. 2010 Nov;40(11):1297-310. PMID 20232240.

39. Minjarez MB, Williams SE, Mercier EM, et al. Pivotal response group treatment program for parents of children with autism. J Autism Dev Disord. 2011 Jan;41(1):92-101. PMID 20440638.

40. Stahmer AC, Akshoomoff N, Cunningham AB. Inclusion for toddlers with autism spectrum disorders: the first ten years of a community program. Autism. 2011 Sep;15(5):625-41. PMID 21486899.

41. Stichter JP, Herzog MJ, Visovsky K, et al. Social competence intervention for youth with Asperger Syndrome and high-functioning autism: an initial investigation. J Autism Dev Disord. 2010 Sep;40(9):1067-79. PMID 20162344.

42. Tanaka JW, Wolf JM, Klaiman C, et al. Using computerized games to teach face recognition skills to children with autism spectrum disorder: the Let's Face It! program. J Child Psychol Psychiatry. 2010 Aug;51(8):944-52. PMID 20646129.

43. Wong VC, Kwan QK. Randomized controlled trial for early intervention for autism: a pilot study of the Autism 1-2-3 Project. J Autism Dev Disord. 2010 Jun;40(6):677-88. PMID 20020319.

44. Rogers SJ, Estes A, Lord C, et al. Effects of a Brief Early Start Denver Model (ESDM)-Based Parent Intervention on Toddlers at Risk for Autism Spectrum Disorders: A Randomized Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2012 Oct;51(10):1052-65. PMID 23021480.

45. Goods KS, Ishijima E, Chang YC, et al. Preschool Based JASPER Intervention in Minimally Verbal Children with Autism: Pilot RCT. J Autism Dev Disord. 2012 Sep 11PMID 22965298.

46. Lerna A, Esposito D, Conson M, et al. Social-communicative effects of the Picture Exchange Communication System (PECS) in Autism Spectrum Disorders. Int J Lang Commun Disord. 2012 Sep;47(5):609-17. PMID 22938071.

47. Chan AS, Sze SL, Han YM, et al. A chan dietary intervention enhances executive functions and anterior cingulate activity in autism spectrum disorders: a randomized controlled trial. Evid Based Complement Alternat Med. 2012;2012:262136. PMID 22666288.

Appendices

Appendix A: Search Strategy

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Strategy

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2011/10/01 to 2012/07/17

LANGUAGE:
English

SEARCH STRATEGY:
autistic[tiab] OR autism[tiab] OR autistic disorder[mh] OR asperger syndrome[mh] OR child development disorders, pervasive[mh:noexp] OR asperger[tiab] OR asperger's[tiab] aspergers[tiab] OR pervasive development[tiab] OR pervasive developmental[tiab] OR pdd[tiab]
AND
therapy[sh] OR therapeutics[mh] OR teaching[mh] OR psychotherapy[mh] OR treatment outcome[mh]

NUMBER OF RESULTS: 44
==========
==========
DATABASE SEARCHED & TIME PERIOD COVERED:
PsycINFO – 2011/10/01 to 2012/07/17

LANGUAGE:
English

SEARCH STRATEGY:
Descriptor: treatment or adjunctive treatment or aftercare or alternative medicine or acupuncture or aromatherapy or faith healing or folk medicine or behavior modification or behavior therapy or aversion therapy or covert sensitization or conversion therapy or dialectical behavior therapy or exposure therapy or implosive therapy or systematic desensitization therapy or reciprocal inhibition therapy or response cost or biofeedback training or classroom behavior modification or contingency management or token economy programs or fading conditioning or omission training or overcorrection or self management or self instructional training or time out or bibliotherapy or cognitive techniques or cognitive restructuring or cognitive therapy or self instructional training or computer assisted therapy or creative arts therapy or art therapy or dance therapy or music therapy or poetry therapy or recreation therapy or crisis intervention services or hot line services or suicide prevention centers or cross cultural treatment or cross cultural counseling or disease management or health care services or continuum of care or long term care or mental health services or community mental health services or palliative care or primary health care or interdisciplinary treatment approach or involuntary treatment or medical treatment general or gene therapy or milieu therapy or movement therapy or multimodal treatment approach or online therapy or outpatient treatment or outpatient

commitment or partial hospitalization or personal therapy or physical treatment methods or acupuncture or artificial respiration or deep brain stimulation or drug therapy or hormone therapy or narcoanalysis or sleep treatment or polypharmacy or vitamin therapy or electrosleep treatment or gene therapy or phototherapy or psychosurgery or thalamotomy or radiation therapy or shock therapy or electroconvulsive shock therapy or insulin shock therapy or surgery or brain stimulation or brain self stimulation or chemical brain stimulation or electrical brain stimulation or spreading depression or transcranial magnetic stimulation or preventive medicine or psychotherapeutic techniques or animal assisted therapy or autogenic training or cotherapy or dream analysis or guided imagery or mirroring or morita therapy or motivational interviewing or mutual storytelling technique or paradoxical techniques or psychodrama or psychotherapy or Adlerian psychotherapy or adolescent psychotherapy or analytical psychotherapy or autogenic training or behavior therapy or aversion therapy or covert sensitization or conversion therapy or dialectical behavior therapy or exposure therapy or implosive therapy or systematic desensitization therapy or reciprocal inhibition therapy or response cost or brief psychotherapy or child psychotherapy or play therapy or client centered therapy or cognitive behavior therapy or acceptance and commitment therapy or eclectic psychotherapy or emotion focused therapy or existential therapy or experiential psychotherapy or expressive psychotherapy or eye movement desensitization therapy or feminist therapy or geriatric psychotherapy or gestalt therapy or group psychotherapy or encounter group therapy or marathon group therapy or therapeutic community or guided imagery or humanistic psychotherapy or hypnotherapy or age regression hypnotic or individual psychotherapy or insight therapy or integrative psychotherapy or interpersonal psychotherapy or logotherapy or narrative therapy or persuasion therapy or primal therapy or psychoanalysis or dream analysis or self analysis or psychodrama or psychodynamic psychotherapy or psychotherapeutic counseling or family therapy or conjoint therapy or rational emotive behavior therapy or reality therapy or relationship therapy or solution focused therapy or supportive psychotherapy or transactional analysis or rehabilitation or cognitive rehabilitation or criminal rehabilitation or drug rehabilitation or alcohol rehabilitation or alcoholics anonymous or detoxification or neuropsychological rehabilitation or occupational therapy or physical therapy or psychosocial rehabilitation or therapeutic social clubs or vocational rehabilitation or supported employment or vocational evaluation or work adjustment training or relaxation therapy or progressive relaxation therapy or sex therapy or social casework or social group work or sociotherapy or speech therapy or treatment guidelines or self help techniques or self management or self instructional training or therapeutic social clubs or medicinal herbs and plants or hypericum perforatum or dietary supplements or diets or nutrition or vitamins or ascorbic acid or choline or lecithin or folic acid or nicotinamide or nicotinic acid

AND

Descriptor: pervasive developmental disorders OR aspergers syndrome OR autism

AND

Publication Type: Peer Reviewed Journal
AND
Population Group: Human
AND
Document Type: Journal Article
AND
Methodology: EMPIRICAL STUDY, -Followup Study, -Longitudinal Study, ---Prospective Study, ---Retrospective Study, FIELD STUDY, -Qualitative Study, -Quantitative Study, TREATMENT OUTCOME/CLINICAL TRIAL
NUMBER OF RESULTS: 59

Appendix B. Evidence Table

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
January 2012 Assessment							
Carter, 2011[3]	RCT	US	Allied health: Language	Hanen's More than Words vs "usual care"	62 toddlers aged 15 to 25 months w ASD	8 group sessions with parents only and 3 in-home individualized parent-child sessions over 3.5 months	At 9 month f/u, there were no main effects of the intervention. There were tx effects on child communication gains that were moderated by children's baseline object interest.
Magiati, 2011[13]	Cohort - 7 year f/u	UK	Behavioral	Autism specific pre-school or community-based EIBI	36 children w ASDs	Mean 30.7 hrs per week, mean length 57.9 months	At 7 year f/u, children were enrolled in varied elementary school programs and had received supplementary interventions such as diet, speech & language therapy, music therapy. Significant increases were found for expressive and receptive language skills raw scores. However, significant decreases in adaptive behavior composite standard scores were found, indicating that although children acquired new skills and abilities over time, they did so a t a rate slower than their typically developing peers.

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Kasari, 2010[7]	RCT	US	Behavioral	Caregiver mediated joint engagement vs wait list	38 toddlers w ASD	24 caregiver-mediated sessions over 8 weeks	At 8 weeks, there was greater improvement on 2 of 3 joint engagement outcomes, one of two joint attention skills outcomes, and one of two play quality outcomes for intervention group. At 12 month f/u gains were either maintained or improved.
Sung, 2011[16]	RCT	Singapore	Behavioral	Cognitive behavioral therapy (CBT) vs Social recreational (SR) program	70 children w ASD and anxiety-related issues, aged 9 to 16 years	One 90 minute group session per week, for 16 weeks	Both groups showed significant reductions in anxiety symptoms at 6 month f/u. No signficant main effect was found for group.
Landa, 2011[10]	RCT	US	Behavioral	Comprehensive intervention vs comprehensive intervention plus "Interpersonal Synchrony" component	48 toddlers w ASD aged 21 to 33 months	6 month intervention. Both groups got 10 hrs per week in classrorom, 1.5 hrs parent training per month, and 38 total hours parent eduacation	A significant effect was found for socially engaged imitation (SEI). The skill was generalized to unfamiliar contexts and maintained thru f/u. Effect on initiation of joint attention was not significant.
Casenhiser, 2011[4]	RCT	Canada	Behavioral	DIR-based developmental social pragmatic (DSP) intervention vs community tx	51 children w ASD aged 24 to 59 months	DSP families given 2 hrs therapy / coaching each week for 12 months	Significant effect on attention to activity, involvement, initiation of joint attention, and enjoyment in interaction. Insignificant effect on standard language assessments.
Konenig, 2010[8]	RCT	US	Social skills	Social skills group using peer tutors vs wait list	44 children aged 8 to 11, with PDD (autism, Asperger's, or PDD NOS), IQ >= 70	School / 75 minutes once per week for 16 weeks	No significant difference on the Social Competence Inventory scales compared w wait list

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Begeer, 2011[2]	RCT	Netherlands	Behavioral	Theory of mind training vs wait list	40 children with ASD aged 8 to 13 years w IQ >70	16 weekly group sessions of 1.5 hrs	Tx group singiicantly improved conceptual Theory of Mind skills, but their elementary understanding, empathic skills and parent reported social behavior did not improve more than control group
Kovshoff, 2011[9]	CCT - 2 year f/u post tx cessation	UK	Behavioral	University EIBI or in home parent commissioned EIBI vs control	41 children w ASDs, 6.5 to 8 years old at f/u	Intervention (described in Remington, 2007) ceased two years earlier	When baseline scores were controlled, there were no statistically significant group effects. However, sub-analysis revealed that parent-commissioned EIBI group maintained some gains
Lee, 2011[12]	Systematic review	Various	Complementary & Alternative (CAM)	Massage therapy	Children w ASDs	Various	One RCT found that massage plus conventional language therapy was superior to language therapy alone for symptom severity and communication attitude. Two RCTs found massage improved sensory profile, adaptive behavior, and language and social abilities compared to a special ed program. A fourth RCT reported effects on social communication.
Rossignol, 2011[15]	Systematic review	Various	Medical & related interventions	Melatonin	Children w ASDs	Dosage only available from inaccessible supplementary material	Meta-analysis of 5 RCTs found significant improvement in sleep onset and duration
Oosterling, 2010[14]	RCT	Netherlands	Parent training	"Focus" training adopting an eclectic approach within a social-pragmatic and developmental context	Children 12 to 42 months old with ASD or PDD-NOS	4 weekly 2 hour sessions with group, followed by a 3 hour home visit every 6 weeks for a year	No significant intervention effects on language, global clinical improvement, or parental skills

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Farmer, 2011[5]	Secondary analysis of Scahill, 2009 RCT	US	Parent training	Parent training added to antipsyc meds vs meds only	124 children w ASD and disruptive behavior, aged 4 to 14 years	Mean 11 60-90 minute sessions over 24 weeks	Higher baseline score on Home Situations Questionnaire (HSQ) predicted greater improvement, regardless of tx. No other child characteristics were significant predictors of improvement, although older children improved slightly more than younger.
Ingersoll, 2011[6]	Case series	US	Parent training	Project ImPACT: School based training for parents	24 children w ASD aged 26 to 70 months, and their parents	6 group and 6 individual coaching sessions over 3 to 4 months	Children used a significantly higher rate of language during free play and home -based routine. Social impairment on the SRS did not decrease significantly on parent report, but did on teacher report
Laugeson, 2011[11]	Controlled trial	US	Social skills	UCLA Peers Program vs delayed tx control	28 adolescents w high functioning ASD and their parents	One 90 minute group session per week, for 14 weeks	Tx group had significantly greater change in parent reported SSRS social skills total, cooperation, assertion and responsibility scale, parent reported SRS total and all SRS scales at tx end. At 14 weeks post tx the vast majority of tx gains were maintained.
February 2012 Assessment							
Hopkins, 2011[22]	RCT	United States	Allied health	FaceSay	49 children with high or low functioning autism	Setting: Computer facility at school Intensity: 10-25m sessions, twice a week for 6 weeks	High functioning children demonstrated improved emotion recognition, social interaction and facial recognition. Low functioning children showed improved emotion recognition and social interactions only.

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Tanaka, 2010[42]	RCT	United States	Allied health	Let's Face It! computer game vs wait list	79 children with ASD and impairment in face processing abilities	Setting: Home Intensity: 20 hours total over 2 to 4 months	Relative to the control group, children in the intervention group demonstrated improvements in recognition of mouth features and holistic recognition of a face based on its eyes.
Lerna, 2012[46]	Controlled Trial	Italy	Allied health	PECS vs Conventional Language Therapy (CLT)	18 preschool children with ASD and little or no functional language	Setting: Within TEACCH program Intensity: A 30 minute individual session 3 times per week for 6 months	Significant difference in favor of the PECS group was reported on the VABS social subscale, but not on ADOS or GMDS (Griffiths' Mental Development Scales).
Wong, 2009[43]	RCT - crossover	China	Behavioral	Autism 1-2-3 early intervention vs wait list	17 children aged 17 to 36 months with ASD	Setting: University Intensity: 10 30-minute sessions over 2 weeks	Intervention group improved in language, communication, reciprocal social interaction, and symbolic play.
Rogers, 2012[44]	RCT	United States	Behavioral	Brief Early Start Denver Model (P-ESDM), Parent delivered vs control	98 children aged 14 to 24 months with ASD	Setting: University / home Intensity: One hour session per week with parents for 12 weeks	There was no effect of group assignment of parent-child interaction or any child outcomes. Both groups improved; younger child age at entrance and greater number of intervention hours were associated with better outcomes.

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Pajareya, 2011[28]	RCT	Thailand	Behavioral	DIR/Floortime vs control	32 preschool children with ASD	Setting: Home (dir/floortime component only), Special preschool for children with ASD (for ongoing ASD interventions) Intensity: 15.2h/week of DIR/Floortime for 3 months	Children receiving DIR/Floortime intervention in addition to their regular curriculum showed significantly greater functional development and (FEAS) and reduction in symptoms of autism (CARS) compared to the control group.
Klintwall, 2012[23]	Case series	Norway	Behavioral	EIBI	21 children between 2-5 years of age with autism	Setting: Clinic Intensity: 20h per week for 12 months	Children who had a larger repertoire of socially mediated and reinforced behaviors benefited more from treatment than children who demonstrated more stereotypical (or automatically reinforced) behaviors
Eikeseth, 2012[19]	Controlled Trial	Norway	Behavioral	EIBI	35 children (2-6 years) with ASD	Setting: Publicly funded mainstream preschools and kindergartens Intensity: 15-37 hours per week (mean 23h, SD 5.3)	EIBI group showed significant improvements in adaptive behaviors, maladaptive behaviors, and autism symptoms after one year of treatment and the gains continued into the 2nd year.

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Eldevik, 2012[20]	Controlled Trial	Norway	Behavioral	EIBI	31 children (2-6 years) with autism	Setting:Mainstream preschool Intensity: 6.5-28 hours per week (mean 13.6h, SD 5.3) for an average of 25 months	Children receiving behavioral intervention had higher IQ scores (Hedges g = 1.03 (95% CI = .34, 1.72) and adaptive behavior composite scores (Hedges g = .73 (95% CI = .05, 1.36).
Strauss, 2012[25]	Controlled Trial	Italy	Behavioral	EIBI	44 children, 26-81m of age, and diagnosed with a diagnosis of either autistic disorder or PPD-NOS	Setting: Center and home Intensity: 25h/week at the center; 10h/week at home	Children receiving EIBI showed improvements in autism severity, developmental and language skills compared to the control group that received eclectic treatment.
Reaven, 2012[24]	RCT	United States	Behavioral	Face Your Fears (Group CBT)	50 youth between 7-14y with ASD	Setting: Not Clear Intensity: 12 sessions each last 1.5h over 4 months	Children receiving CBT showed significant improvement in clinician rated autism severity, diagnostic status, and clinician rated global improvement.
Goods, 2012[45]	RCT	United States	Behavioral	JASPER (Joint Attention Symbolic Play Engagement and Regulation) vs treatment as usual	15 preschool children with ASD	Setting: University 30 hour per week ABA program Intensity: Two 30 minute sessions per week, for 12 weeks	Tx group had greater play diversity on standardized assessment. In classroom , tx group initiated more gestures and spent less time unengaged.

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Kaale, 2012[35]	RCT	Norway	Behavioral	Joint Attention at preschool vs preschool alone	61 preschoolers with autism	Setting: Preschool Intensity: Two 20 minute sessions, 5 days per week, for 8 weeks	Intervention group showed significantly more joint attention with preschool teachers and longer duration of joint engagement with mothers.
Flanagan, 2012[21]	Controlled Trial	Canada	Behavioral	Ontario IBI	142 children with autism	Setting:Self contained treatment centers in the community or in children's homes Intensity:20-35h/week.	Children in the IBI group showed improved outcomes including lower severity of autism, higher adaptive functioning and cognitive skills.
Ingersoll, 2010[34]	RCT	United States	Behavioral	Reciprocal Imitation Training vs control	21 children aged 27 to 47 months with autism	Setting: "Treatment room" Intensity: 3 hours per week for 10 weeks	Controlling for initial imitation performance, the TX group made significantly more gains in elicited imitation and spontaneous imitation than the control group
Minjarez, 2010[39]	Case series	United States	Behavioral -Parent delivered	Pivotal Response Training (PRT)	17 families with a child with ASD with language delay	Setting: University Intensity: One 90 minute group session for parents per week for 10 weeks, plus a single 50 minute individual session	Primary outcome - child functional verbal utterances - increased significantly from baseline to week 10.

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Alcantara, 2011[17]	Systematic review	Various	CAM	Chiropractic/spinal manipulation	Children <=18 years diagnosed with ASDs	Setting: Various Intensity: Various	Only 5 studies (3 case reports, 1 cohort, 1 RCT) were retrieved leading the authors to concluded that there was insufficient evidence to draw any efficacy related conclusions.
Chan, 2012[47]	RCT	China	CAM	Shaolin diet vs usual food	24 children aged 7 to 17 with ASD	Setting: Home Intensity: One month	Intervention group had significantly improved mental flexibility and inhibitory control. Standard assessments (SRS, SSRS, ADOS, VABS) not used.
Stahmer, 2011[40]	Case Series F/u of Stahmer & Ingersoll, 2004	United States	Educational	Childrens Toddler School (CTS)	102 children with ASD	Setting: Inclusive classroom Intensity: 5 to 15 months, 15 hours per week in class, 4 hours per week individual service	31% of children entering with ASD were functioning in the "typically developing" range when they finished the program at age 3. Significant gains in adaptive behavior and communication were reported.
Dunst, 2011[33]	Case series	United States	Educational	Interest-based learning	17 preschoolers with autism	Setting: Home Intensity: Varies depending on activities of interest, at least weekly	The high interest-based group made significantly more progress on language, cognitive, and social subscales of the parent Developmental Observation Checklist System (DOCS)

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Strain, 2011[27]	RCT	United States	Educational	LEAP	177 pre-schoolers, mean age 50m with a diagnosis of ASD	Setting: Preschool classroom Intensity: Various based on individual needs. Intervention lasted 2 years.	Children receiving LEAP training in classrooms demonstrated improvements in symptoms of autism, reductions in problem behavior and higher cognitive, language, and social skills.
Boyd, 2012[29]	Controlled Trial	United States	Educational	TEACCH vs LEAP vs control	205 children with autism	Setting: Classroom Intensity: NR	Preliminary results indicate no significant differences across children receiving TEACCH or LEAP and the control group.
Bent, 2011[30]	RCT	United States	Medical & related interventions	Omega-3 Fatty Acids versus placebo	27 children aged 3 to 8 with autism and hyperactivity	Setting: Outpatient Dosage: 1.3 grams/ day	Difference in hyperactivity between placebo and Omega- 3 group not significant
Kasari, 2012[26]	RCT	United States	Social Skills	Child- and/or peer-mediated social skills intervention	60 children 6-11y of age with a diagnosis of ASD	Setting: School Intensity: 12 sessions each lasting 20min, twice a week for 6 weeks	Significant improvement in network salience, no. of friendship nominations, teacher reported social skills and reduction in playground isolation in children receiving peer mediated social skills training.

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Lopata, 2010[38]	RCT	United States	Social Skills	*Skillstreaming* group program vs wait list	36 children aged 7 to 12 with HFA	Setting: University Intensity: 5 daily 70 minute treatment cycles, 5 days per week, for 5 weeks, plus one weekly 90 minute parent training	Mean difference in both parent and staff completed SRS (Social Responsiveness Scale) and DANVA2 (Diagnostic Analysis of Nonverbal Accuracy) was significantly higher in intervention group
Stichter, 2010[41]	Case series	United States	Social Skills	Social competence intervention (SCI)	27 male students aged 11 to 14 with Aspergers / HFA	Setting: University Intensity: One hour, twice weekly for 10 weeks	Intervention group made significant gains on all subscales of SRS and DANVA
de Bruin, 2012[18]	Case series	The Netherlands	Social Skills	Social Skills (specifically the Dutch"Spelend Leren, Leren Spelen" protocol)	10 children ages 8-9 years diagnosed with PDD-NOS	Setting: University outpatient department of Child Psychiatry Intensity: 1.5 hours per session for 14 session over 6 months. Includes 2 additional follow up sessions of unspecified duration.	Significant differences were noted in the scores of the "Scholastic Competence," and "Physical Appearance" subscales of the SPPC indicating changes in their self perception profile. Parent's showed significant improvement in the CSBQ scale.
DeRosier, 2010[32]	RCT	United States	Social Skills	Social skills group for HFA vs. generic social skills group	55 children aged 8 to 12 with high functioning autism	Setting: Group Intensity: 15 weekly one hour sessions; parent attended 4 of these	HFA targeted intervention group showed significant improvement in awareness, communication, motivation, and mannerisms SRS scales compared to generic intervention group

Author, Year	Study Design	Country	Intervention Category	Specific Intervention	Population	Setting / Intensity	Outcomes
Castorina, 2011[31]	Controlled Trial	Australia	Social Skills	Social skills training, with or without sibling participation vs wait list control	21 boys aged 8 to 12 with Asperger syndrome	Setting: Group Intensity: 8 weekly 2 hour sections	No difference in parent or teacher SRSS between groups. Subjects identification of non-verbal social cues significantly improved and was maintained at 3 month follow-up.
Karkhaneh, 2012[36]	Systematic review	Various	Social Skills	Social stories	135 children aged 4 to 14 with autism	Setting: Varies Intensity: Varies	5 of the 6 controlled trials identified showed significant benefits regarding social interaction
Lerner, 2011[37]	Controlled Trial	United States	Social Skills	Socio-dramatic Affective-Relational Intervention vs control	17 adolescents with Asperger syndrome	Setting: Community social service agency Intensity: 6 week summer program	Intervention group showed greater improvement and post-TX maintenance on social assertion and the ability to detect emotion in adult voices

Legend: ASD- Autsim Spectrum Disorder; CAM-Complementary and Alternative Medicine; CBT-Cognitive Behavioral Therapy; CCT- Central Conduction Time_; DSP-developmental social pragmatic; EIBI- Early Intensive Behavioral Intervention (EIBI); PDD- **Pervasive Developmental Disorder** ; PDD-NOS- **Pervasive Developmental Disorder-Not Otherwise Specified** ; RCT- Randomized Controlled Trial; SEI-Socially Engaged Imitation; SR-Social Recreational; SRS-Sorical Responsiveness Scale; SSRS-Social Skill Rating System

Appendix C. Questionnaire Matrix

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: Effects of Treatment on Core and Commonly Associated Symptoms in Children With ASDs: Behavioral Interventions			
Behavioral interventions. Early intensive behavioral and developmental intervention may improve core areas of deficit for individuals with ASDs; however, few randomized controlled trials (RCTs) of sufficient quality have been conducted, no studies directly compare effects of different treatment approaches, and little evidence of practical effectiveness or feasibility exists.	☐	New Evidence:	☐
Studies of UCLA/Lovaas-based interventions report greater improvements in cognitive performance, language skills, and adaptive behavior skills than broadly defined eclectic treatments available in the community. However, strength of evidence is currently low. Further, not all children receiving intensive intervention demonstrate rapid gains, and many children continue to display substantial impairment.	☐	New Evidence:	☐
Although positive results are reported for the effects of intensive interventions that use a developmental framework, such as the Early Start Denver Model (ESDM), evidence for this type of intervention is	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
currently insufficient because few studies have been published to date.			
Less intensive interventions providing parent training for bolstering social communication skills and managing challenging behaviors have been associated in individual studies with short-term gains in social communication and language use. The current evidence base for such treatment remains insufficient, with current research lacking consistency in interventions and outcomes assessed.	☐	New Evidence:	☐
Although all of the studies of social skills interventions reported some positive results, most have not included objective observations of the extent to which improvements in social skills generalize and are maintained within everyday peer interactions. Strength of evidence is insufficient to assess effects of social skills training on core autism outcomes for older children or play- and interaction-based approaches for younger children.	☐	New Evidence:	☐
Several studies suggest that interventions based on cognitive behavioral therapy are effective in reducing anxiety symptoms. Strength of evidence for these interventions, however, is insufficient pending further	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
replication.			
Educational interventions. Most research on the Treatment and Education of Autistic and Communication related handicapped CHildren (TEACCH) program was conducted prior to the date cutoff for our review. Newer studies continue to report improvements among children in motor, eye-hand coordination, and cognitive measures. The strength of evidence for TEACCH, as well as broad-based and computer-based educational approaches to affect any individual outcomes is insufficient because there are too few studies and they are inconsistent in outcomes measured.	☐	New Evidence:	☐
Medical and related interventions. Although no current medical interventions demonstrate clear benefit for social or communication symptoms, a few medications show benefit for repetitive behaviors or associated symptoms.	☐	New Evidence:	☐
The clearest evidence favors the use of medications to address challenging behaviors. The antipsychotics risperidone and aripiprazole each have at least two RCTs demonstrating improvement in a	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
parent-reported measure of challenging behavior. A parent reported hyperactivity and noncompliance measure also showed significant improvement. In addition, repetitive behavior showed improvement with both risperidone and aripiprazole. Both medications also cause significant side effects, however, including marked weight gain, sedation, and risk of extrapyramidal symptoms (side effects, including muscle stiffness or tremor, that occur in individuals taking antipsychotic medications). These side effects limit use of these drugs to patients with severe impairment or risk of injury.			
We rated the strength of evidence as high for the adverse effects of both medications, moderate for the ability of risperidone to affect challenging behaviors, and high for aripiprazole's effects on challenging behaviors.	☐	New Evidence:	☐
Allied health. The allied health interventions reviewed here varied; the research provided little support for their use.	☐	New Evidence:	☐
Specifically, all studies of sensory integration and music therapy were of poor quality, and two fair-quality studies of		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
auditory integration showed no improvement associated with treatment.	☐		☐
Language and communication interventions (Picture Exchange Communication System [PECS] and Responsive Education and Prelinguistic Milieu Training [RPMT]) demonstrated short-term improvement in word acquisition without effect durability, and should be studied further. No other allied health interventions had adequate research to assess the strength of evidence.	☐	New Evidence:	☐
CAM. Evidence for CAM interventions is insufficient for assessing outcomes.	☐	New Evidence:	☐
Key Question 2. Modifiers of Treatment Outcomes			
With rare exceptions, few studies are designed or powered to identify modifiers of treatment effect. Although we sought studies of treatment modifiers, only one included study actually demonstrated true treatment modifiers based on appropriate study design and statistical analysis. One other study was designed to examine the role of provider on outcomes but showed no difference, possibly because it was	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
underpowered to do so.			
This first study included an analysis of initial characteristics of the children, demonstrating that children who were low in initial object exploration benefited more from RPMT, which explicitly teaches play with objects, while children who were relatively high in initial object exploration demonstrated more benefit from PECS. An additional analysis showed greater increases in generalized turn-taking and initiating joint attention in the RPMT group than in PECS. The increased benefit in joint attention for RPMT was seen only in children who began the study with at least seven acts of joint attention.	☐	New Evidence:	☐
One study explicitly sought to examine the impact of provider (parent vs. professional) using similar interventions in an RCT. The study did not show a difference in outcomes for children receiving the UCLA/Lovaas protocol-based intervention in a clinical setting vs. at home from highly trained parents.	☐	New Evidence:	☐
Other studies identified potential correlates that warrant further study. Modifiers with potential for further investigation but with currently conflicting data included pretreatment IQ and language skills, and	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
age of initiation of treatment (with earlier age potentially associated with better outcomes). Social responsiveness and imitation skills have been suggested as skills that may correlate with improved treatment response in UCLA/Lovaas treatment, whereas “aloof ” subtypes of ASDs may be associated with less robust changes in IQ. Other studies have seen specific improvement in children with PDD-NOS vs. Autistic Disorder diagnoses, which may be indicative of baseline symptom differences. However, many other studies have failed to find a relationship between autism symptoms and treatment response.			
Key Question 3: Early Results in the Treatment Phase That Predict Outcomes			
The literature offers almost no information about specific observations of children that might be made early in treatment to predict long-term outcomes. Some evidence suggests that changes in IQ over the first year of either UCLA/Lovaas-based or ESDM intervention predicts, or accounts for, longer term change in IQ. However, findings also suggest that although gains in the cognitive domain might be identified primarily within the first year of treatment, changes in adaptive behavior in response to	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
these same interventions may occur over a longer timeframe, if they occur at all.			
Key Question 4: End of Treatment Effects That Predict Outcomes			
One study specifically addressed end-of-treatment effects to predict longer range outcomes. The feasibility of such studies was established in this language study, which reported outcomes 12 months postintervention.	☐	New Evidence:	☐
Key Question 5: Generalization of Treatment Effects			
Few studies measured generalization of effects seen in treatment conditions to either different conditions or different locations. Among behavioral studies, those of treatments for commonly associated conditions, such as anxiety, employed outcomes assessment outside the therapeutic environment, with positive results observed. However, in most cases, outcomes are parent reported and not confirmed by direct observation.	☐	New Evidence:	☐
For medical studies, data across classes of medications are likely to be transferable outside of the clinic setting, primarily because the outcome measures used in these studies rely on parent report of the subjects' behavior in the home or other settings and	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
are augmented in some studies by teacher report.			
Key Question 6: Drivers of Treatment Effects			
No studies were identified to answer this question.	☐	New Evidence:	☐
Key Question 7: Treatment Approaches in Children Under Age Two at Risk for Diagnosis of ASDs			
Research on very young children is preliminary, with four studies identified. One good-quality RCT suggested benefit from the use of ESDM in young children, with improvements in adaptive behavior, language, and cognitive outcomes. Diagnostic shifts within the autism spectrum were reported in close to 30 percent of children but were not associated with clinically significant improvements in ADOS severity scores or other measures.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			